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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,193	06/20/2005	Dulce Elena Casarini	0002150USU/2417	2762

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OHLANDT, GREELEY, RUGGIERO & PERLE, LLP
ONE LANDMARK SQUARE, 10TH FLOOR
STAMFORD, CT 06901

EXAMINER	
CHEU, CHANGHWA J	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
01/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,193	CASARINI ET AL.	
	Examiner	Art Unit	
	JACOB CHEU	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

2. Applicant's amendment filed on 11/17/2008 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

Claims 1-26 have been cancelled.

Claims 27-45 are added.

Claims 27-45 are under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 27-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

> With respect to claim 27, the method is not complete. It is not known the relationships of these ACEs with respect to the development of the hypertension disease. More detailed steps are needed for clarification. Similarly, claim 37 suffers the same problem as claim 27. It is needed to identify which ACEs isoform(s) would be higher/or lower compared to the normal healthy population.

Claim Rejections - 35 USC § 112

Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 37-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The instant invention directs to methods of identification and quantification of proteins, isoforms of angiotensin I converting enzyme (ACE), specifically ACE of 190-kDa, specially of 90 kDa and of 65 kDa in tissues, cells and biological fluids, specially in urine, a molecular marker based on said proteins, use of mentioned molecular marker, analytical method for diagnosis, risk stratification, therapeutical decision in carriers of arterial hypertension and primary or secondary renal lesion and kit for using in the diagnosis.

However, in view of the experimental method and results, there is no support of using the above mentioned ACE isoform biomarkers as indicators of renal damage.

Based on the experiments, Applicant concluded in several places indicating that the 65, 90, 190 kDa, are ACE isoforms. Particularly, the 90 kDa only appear in the hypertensive patients, and could serve as a biomarker for hypertension diagnosis (See page 25, line 12-16; page 32, line 12-16; page 38, line 1-6). The only data refer to the organ are Table II, yet these data are not for organ damage, but for tissue ***distribution*** in adrenal, aorta, heart, lung, and kidney. No method or guidance of which organ or what criteria to measure organ damage is disclosed (emphasis added). It is noted that Applicant makes an extrapolation based on Applicant's 1997 where Applicant concluded that the ACE activity in urine is not from plasma but from the renal tubule. Furthermore, Applicant also relies on Baggio et al. (Clin Chim Acta 1981 Vol. 109, page 211-218) and Kato et al. (J. Clin.Chem Chin Biochem 1982 Vol. 20, page 473-476) studies and concluded that since there is a considerable level increasing in renal and infectious of upper urinary disease, the ACE can be used as an indicator for renal damage (See specification section 0042. In view of the main claim 37, the recited method teaches using at least three angiotensin converting enzyme isoforms as a biomarkers for renal damage analysis. However, the current application merely uses three biomarkers, namely 190, 90 and 65 kDa for analysis. There are also 170, 140, 130, 59, 94, 55 and 57 kDa isoform exist (See Section 0042 in the specification). There is no discussion nor experimental data is disclosed to the above mentioned different ACE isoforms. It is not known whether any of them contributing or associating with the renal damage. In addition, it is not known whether there is a *correlation* between the increased ACE activity and the level of the current 190, 90 and 65 kDa (emphasis added). No reasonable extrapolation with respect to the appearance of these isoforms can be inferred. More experiments would inevitably be needed in order to further verify the correlation of these particular biomarkers and the appearance of the renal damage.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 27-31, 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casarini et al. (Intl. J. Biochem. Cell Biology 2001 Vol. 33, page 75-85).

> Casarini et al. teach a method of identifying and quantifying of isoforms of angiotensin I converting enzymes (ACE) in biological fluids, e.g. urine (See Abstract). Casarini et al. teach collecting an aliquot of concentrated urine and submiting the samples to separation and Western blot analysis (See page 76 Method and Figure 5 for Western blot analysis). Casarini et al. identify different ACE isoforms, such as 65 kDa, 90 kDa and 190 kDa (See Abstract; page 79, right column first paragraph; Figure 5) where the 190 kDa and 65 kDa are in normal individuals, and 90 kDa appears in hypertension people. supra.

Although Casarini et al. do not explicitly teach these are "*makers*" in characterizing the hypertension in individuals, one ordinary skill in the art in reviewing the teachings of Casarini, would have been motivated to use the 65, 90 and 190 kDa ACE isorforms as the markers for evaluating hypertensive disease in patients with reasonable expectation of success because the reliability of sufficient sample size analysis conducted by Casarini et al. (80 patients), and the different profiling, i.e. 65, 90 and 190 kDa ACE isoforms, appears between normal and hypertension patients. Furthermore, with the readily available specific antibodies recognizing these 65, 90 and 190 ACE isoforms through the Western blot analysis, it merely requires routine practice in the field to screen the biological samples from the patients to identify the presence of the ACE isoforms.

With respect to claims 29, 90 kDa is present in the biological fluid, i.e. urine, of the hypertensive patients, and thus can be a marker of a predisposed hypertension. Supra.

With respect to claim 31, Casarini et al. teach using Western blot where specific antibodies against somatic ACE isoform of 190 kDa and against N-domain of ACE isoform of 65 and 90 kDa are used for identification (See Figure 5).

4. Claims 32-33 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casarini et al. as applied to claim 27, and further in view of Acton et al. (US 20050147600).

Casarini et al. reference has been discussed and Casarini et al. teach using antibody, HPLC chromatography to identify the ACE isoform. However, Casarini et al. do not disclose applying mass spectroscopy to identify ACEs.

Acton et al. teach identifying ACE by mass spectroscopy (See Section 412).

Therefore, it would have been prima facie obvious to one ordinary skill in the art at the time the invention was made to have motivated Casarini et al. to apply mass spectroscopy , such as taught by Acton, to identify the ACEs in the sample. One ordinary skill in the

art would have been motivated to do so since mass spectroscopy is well-known and widely used in the field for its accuracy, particularly molecular weight based identification. One ordinary skill in the art would have combined both HPLC and mass spectroscopy for identification of the ACEs in the sample for better and more accurate result.

With respect to claim 34, Casarini et al. also show that the two peaks eluted by chromatography, corresponding to 65 kDa and 190 kDa in normotensive individuals and and 65 kDa and 90 kDa appear in hypertensive patients (See Figure 5; page 83, right column, third paragraph and page 84, first paragraph; also the cited reference 19).

Response to Applicant's Arguments

With respect to new claims 27 and 37, Applicant briefly describes the recited features from the specification.

With respect to claim 27 " The claimed method of detecting a predisposition for developing hypertension in an individual comprising the step of detecting the presence of three angiotensin converting enzyme

("ACE") isoforms is supported in the Specification at least in paragraphs [0067] and [0068]. Both of these paragraphs disclose that normotensive individuals with hypertensive parents who presented the three ACE isoforms (65kDa, 90kDa, and 19kDa) were predisposed to develop hypertension later in life. On the other hand, normotensive individuals should only present the 65kDa and 190kDa, while hypertensive individuals present only the 65kDa and 90kDa isoforms. As such, the presence of the 90kDa isoform can be regarded as a marker for hypertension and the combination of the three isoforms indicates a predisposition to develop hypertension."

With respect to claim 37, "The claimed method of detecting a predisposition for the development of a kidney lesion in an individual, comprising detecting and quantifying the presence of the 65kDa, 90kDa, and 190kDa ACE isoforms, is supported in the Specification at least in paragraphs [0042] and [0095]. The Specification discloses that the ACE activity in urine is produced by the kidney, and that any considerable increase of ACE activity can be used as a marker for detecting renal lesions. In addition, it is suggested that the high concerntration of ACE in urine was due to the local secretion site of this enzyme in the kidney (duct collector). In addition, the Specification discloses in Table II, the tissue ACE activity distribution in adrenal, aorta, heart, liver, lung, kidney and testicles. This further supports the idea that these tissues are capable of producing ACE isoforms."

Concerning the above statement, Examiner has set forth rejection outlined in this Office Action (See above). For the claim 27, it is under 35 USC 103 (a), for claim 37, it is under enablement rejection under 35 USC 112, first paragraph.

5. The reference of Hattori et al. has been withdrawn because Hattori et al. using premature infant samples which could not reflect hypertension patients.

6. Applicant argues that Casarini et al. merely use two ACE isoforms, namely 65 and 90 kDa for detecting hypertensive patients.

Applicant's arguments have been considered, but are not persuasive.

It is noted that the samples of Casarini et al. are from hypertensive patients (See page 76, right column, Methods). The conclusion of Casarini et al. is the ***same*** as the instant

invention (also see Remarks, above), that 90 kDa has an important role in development of hypertension (See abstract)(emphasis added). Casarini et al. indicate that *the 90 kDa (HP2 ACE) is different from high molecular weight (190 kDa) and LMW (65 kDa) normal ACEs*. (See Abstract)(emphasis added). Therefore, the study of Casarini et al. is analogous and applicable for detecting predisposition of development of hypertension in an individual. It would have been obvious to one ordinary skill in the art to compare all three ACEs in order to have a more thorough and accurate profiling for assessing the hypertensive patients.

Conclusion

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JACOB CHEU whose telephone number is (571)272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jacob Cheu/
Examiner, Art Unit 1641